SPLENIC STUDIES

I. SUSCEPTIBILITY TO INFECTION AFTER SPLENECTOMY PERFORMED IN INFANCY*

HAROLD KING, M.D., AND HARRIS B. SHUMACKER, JR., M.D.

INDIANAPOLIS, IND.

FROM THE DEPARTMENT OF SURGERY, INDIANA UNIVERSITY MEDICAL CENTER, INDIANAPOLIS

AMONG APPROXIMATELY 100 splenectomies performed at the Indiana University Medical Center, five have been carried out in infants under the age of six months. It is specifically with this group of five cases, and more particularly with their susceptibility to infection after operation, that this paper is concerned. Four of the five infants developed either meningitis or overwhelming meningococcemia in from six weeks to three years after operation and one of the four died of the infection. The fifth child was returned to the hospital a few days after discharge following splenectomy with a rapidly fatal febrile illness, suggestively infectious in nature.

In an effort to learn whether this extraordinary association of splenectomy in infancy and subsequent susceptibility to severe infection had been observed by others, the literature dealing with splenectomy was carefully reviewed. Little pertinent information was obtained. The age at which the operation was performed is not mentioned in many reports and in only a very few instances is it stated that splenectomy was carried out during the first six months of life. Furthermore, most of the reports do not include sufficiently long follow-up studies to establish or rule out subsequent serious infection. One interesting account[2] was found, however, of a premature infant born at 35 weeks of gestation and treated by splenectomy 14 hours after birth for acute thrombocytopenic purpura. The child made a good recovery from the operation and the platelet count rose to a normal level. The baby continued to do well until the twenty-first postoperative day, when there suddenly developed an overwhelming bacteremia. Death occurred in spite of intensive antibiotic therapy. Postmortem examination revealed only evidence of severe sepsis.

CASE REPORTS

Each of the five cases had a well established diagnosis of congenital hemolytic anemia with typical hematologic picture including the presence of spherocytes and evidence of increased erythrocyte fragility. In four of the five cases there was a family history of congenital hemolytic anemia. In each case splenectomy was carried out with ease and, when present, accessory spleens were removed. The five cases include two pairs of siblings. In neither case, however, did the infection in the two siblings occur at the same time and, consequently, there was not present the problem of transference of infection from one to the other.

Case 1.—The patient was admitted to the hospital at 3 weeks of age. His mother had had a splenectomy for congenital hemolytic icterus. He was slightly jaundiced and the spleen was palpable. There was anemia of severe degree. After a number of blood transfusions, splenectomy was performed on the twelfth day of his hospital stay. The postoperative course was excellent, with prompt rise of hemoglobin and red blood count to relatively normal limits.

* Aided in part by a grant from the James Whitcomb Riley Memorial Association. Submitted for publication October, 1951.

Approximately 1 year after the first admission the patient, now twelve and a half months old, was re-admitted to the hospital. He was acutely ill. The temperature was 104°F. There was nuchal rigidity and a petechial rash was present over most of the body. The spinal fluid contained 4000 leukocytes per cu. mm. and meningococci were found in cultures of the blood and spinal fluid. The patient was treated vigorously with sulfadiazine and penicillin and made an uneventful recovery.

Case 2.—This patient, a sister of the patient in Case 1, was born in the hospital and was noticed to have jaundice the following day. The spleen was enlarged. After a number of transfusions splenectomy was performed when the child was 3 weeks old. The postoperative course was uncomplicated.

She was re-admitted at the age of 6 months. There was a five-day history of fever and irritability which had improved temporarily following a short course of sulfadiazine therapy. On admission to the hospital the infant was acutely ill and had marked nuchal rigidity. The spinal fluid contained 417 leukocytes per cu. mm. However, no bacteria were found on smear or culture. The patient was treated with penicillin and sulfadiazine and gradually recovered. The final diagnosis was meningitis, causative organism undetermined.

Case 3.—This patient was admitted to the hospital at 3 days of age because of jaundice of 1 day's duration. His father had had a splenectomy for congenital hemolytic icterus. The spleen was enlarged. Splenectomy was performed when the infant was 15 days old. The immediate postoperative course was excellent.

The patient was next admitted at the age of 2½ months because of paroxysms of coughing. A diagnosis of whooping cough was made. Recovery was prompt. When the child was six months old there was a third admission to the hospital, necessitated by diarrhea for which no specific organism was found. She recovered without difficulty and was discharged two weeks later in good condition.

At the age of eight and a half months she was admitted for the fourth time with a 12-hour history of irritability, a convulsive seizure and a petechial rash on the face and body. She was obviously acutely ill. A diagnosis of meningococcemia was made and intravenous sulfadiazine and penicillin therapy was begun, but the patient died a few hours after admission to the hospital. Both blood cultures and spinal fluid cultures were positive for meningococci. Autopsy revealed no evidence of meningitis. Both suprarenal glands were found to be markedly hemorrhagic. The final postmortem diagnosis was meningococcemia associated with the Waterhouse-Friderichsen syndrome.

Case 4.—This patient, a brother of the patient in Case 3, was first admitted at the age of 5 months because of severe anemia. The spleen was palpable at the level of the umbilicus. After a number of transfusions splenectomy was carried out. He was then approximately 6 months old. The postoperative course was uneventful and the hemoglobin and erythrocyte count promptly rose to a relatively normal level.

The child was next admitted at the age of 2½ years with a two-day history of pharyngitis and fever. He was irritable, lethargic and had a right lateral nystagmus. These findings cleared rapidly without specific therapy, and although encephalitis was suspected a definite diagnosis was not established.

He was re-admitted a year later when he was three and a half years old. For 2 weeks he had complained of a sore throat and episodes of stiffness of the neck. He had been treated with penicillin and sulfadiazine. Physical examination at the time of admission revealed nuchal rigidity. The patient was found to have meningitis due to *Hemophilus inflenza,* type B. He was placed on dihydrostreptomycin and sulfadiazine and made an uneventful recovery.

Case 5.—The patient was first admitted at the age of 13 days because of jaundice of 5 days' duration. The spleen was enlarged. Splenectomy was performed when the child was two and a half months old. She was apparently doing quite well until the seventh postoperative day when a dehiscence of the abdominal wound occurred. The wound was immediately re-sutured and the baby seemed to suffer no ill effects. About two weeks later she was discharged.

Two days after the baby left the hospital she developed a low grade fever and vomiting. On the following day the temperature rose to 104° and the patient's physician gave her penicillin. On the next day the baby was re-admitted to the hospital. She was acutely ill and severely dehydrated. The temperature was 103° and the leukocyte count 29,400. Penicillin, oxygen, whole blood, plasma and intravenous fluids were given, but the patient died on the third hospital day at the age of three and a half months. Permission for autopsy was refused, and a definite cause of death was not clearly established.

DISCUSSION

Though our series of cases in which splenectomy was performed during the first six

months of life is small, the subsequent development of serious infection was so constant as to suggest a cause-effect relationship. It is hoped that experiences of others with splenectomy in infancy will be reviewed in order to substantiate or refute this apparent relationship. Unless additional data should cast doubt upon it, one would be forced to assume that splenectomy in infancy is followed by an increased susceptibility to infection.

Why serious infection apparently tends to follow splenectomy performed in infancy and not in patients splenectomized at an older age is certainly far from clear. It is well known, of course, that age profoundly affects the function of many of the organs of the body. There is some evidence recorded in the literature tending to show that splenic activity varies with age. Gross[1] studied 111 spleens obtained at autopsy and from the many anatomical and pathologic changes noted from birth to old age concluded that the spleen probably has its greatest functional activity very early in life. Marine[4] found that age is an important factor in the growth of splenic autografts, and he also concluded that this organ is most important in early life.

There is a large body of literature concerning the relationship of the spleen to resistance to infection. This evidence may be grouped into four categories:

1. Since antiquity, it has been known that the spleen tends to enlarge in the presence of certain infections. The results of postmortem examination in a variety of infections have shown that the spleen responds to infection with congestion, cellular infiltration, proliferation of the cells of the macrophage system and hyperplasia of lymphatic tissue.

2. Many latent infections are reactivated following splenectomy. One example of this phenomenon is that of Bartonella muris infection of rats. It has, however, been observed in many different animals that a number of types of latent infection are reactivated following splenectomy. Mice, squirrels, horses, cattle, apes, and other animals have shown conversion of latent infection into manifest disease following removal of the spleen.[7]

3. There is some suggestive evidence that in certain animal species splenectomy depresses the natural resistance to acute and chronic infections. Morris and Bullock[6] studied the effect of splenectomy in the rat on the mortality from a spontaneously acquired infection with *Bacterium enteritidis* (Gaertner). They concluded that removal of the spleen temporarily diminishes the natural resistance of the rat to infection. As an example of data obtained by them may be cited one experiment in which 72 immature rats were splenectomized while another 72 were castrated as controls. During a period of two months' observation 85 per cent of the splenectomized rats succumbed to *Bacterium enteritidis* infection, and only 29 per cent of the control group. Marmorston[5] performed a similar experiment on mice and concluded that splenectomy in a strain highly resistant to infection depresses the natural resistance of these animals to subsequently introduced acute bacterial infection (*Bacterium enteritidis*).

4. Since the spleen is the largest single reservoir of lymphocytes in the body and since the lymphocytes have been demonstrated to have a major role in antibody formation, the spleen would appear to play a leading part in this important defense function. Rowley[3] recently carried out experiments on the splenectomized rat in order to determine whether immunologic responses were altered. He found that if a small amount of antigen is given intravenously, the splenectomized rat responds with a low circulating antibody titer, whereas high titers are obtained in non-splenectomized animals. He also[8] studied human subjects and found that 13 of 14 splenectomized patients failed to respond with a significant

rise in antibody titer after the intravenous injection of antigen while, in contrast, all of the control subjects responded with a significant rise in antibody titer.

In spite of the known relationship of the spleen to antibody formation and its demonstrated role in resistance to infection in certain animal species, no significant hazard of infection appears to follow splenectomy in human adults or children. Our experience would suggest, however, that when splenectomy is performed during the first few months of life there may follow, at least for a time, an increased susceptibility to infection. This suggestive experience has prompted us to undertake animal experiments which it is hoped may throw additional light upon the problem. It certainly makes it desirable to analyze other clinical material in order to establish or rule out the casual relationship between the removal of the spleen in infants and the serious infections we have observed to follow this procedure.

BIBLIOGRAPHY

[1] Gross, L.: Studies on the Gross and Minute Anatomy of the Spleen in Health and Disease. J. Med. Res., **39:** 311, 1919.

[2] Gruber, S., B. Redner and B. Kogut: Congenital Idiopathic Thrombocytopenic Purpura in a Premature Infant with Splenectomy. New York State J. Med., **51:** 649, 1951.

[3] Harris, T. N., E. Grimm, E. Merteus and W. E. Ehrich: The Role of the Lymphocyte in Antibody Formation. J. Exper. Med., **81:** 73, 1945.

[4] Marine, D., and O. T. Manley: Homeotransplantation and Autotransplantation of the Spleen in Rabbits. J. Exper. Med., **32:** 113, 1920.

[5] Marmorston, J.: The Effect of Splenectomy on Acute Bacterium Enteritidis Infections in White Mice. Proc. Soc. Exper. Biol. & Med., **32:** 981, 1935.

[6] Morris, D. H., and F. D. Bullock: The Importance of the Spleen in Resistance to Infection. Ann. Surg., **70:** 513, 1919.

[7] Perla, D., and J. Marmorston: The Spleen and Resistance. Baltimore, 1935, The Williams and Wilkins Co.

[8] Rowley, D. A.: The Effect of Splenectomy on the Formation of Circulating Antibody in the Adult Male Albino Rat. J. Immunol., **64:** 289, 1950.

[9] ———: The Formation of Circulating Antibody in the Splenectomized Human Being Following Intravenous Injection of Heterologous Erythrocytes. J. Immunol., **65:** 515, 1950.

ADDENDUM

Since preparation of this manuscript we have learned through correspondence with Dr. C. C. Ferguson that nine infants with congenital hemolytic anemia, treated at The Children's Medical Center, Boston, by splenectomy at six months of age or earlier have developed no serious infection during a follow-up period ranging from one to six years. One child treated at seven and a half months of age did die one year later of tracheo-bronchitis. Grouping together the patients of Gruber, Redner and Kogut, our own cases and those of Ferguson, the incidence of serious infection and death occurring after splenectomy carried out within the first six months of life is still alarmingly high. Serious illness has occurred in six of the 15 patients, and three of them have died.